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MSK.P-035-US
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant: Sadelain et al.

Serial No.: 08/940,544 Examiner: L. Helms

Filed: September 30, 1997 Art Unit: 1642

For: Fusion Proteins of a Single-Chain Antibody and CD28 and Uses Thereof

RESPONSE TO OFFICIAL ACTION

Asst. Commissioner for Patents

Washington, D.C. 20231

Sir:

This is in response to the Official Action mailed October 9, 2002 for the above-captioned application. Applicants request an extension of time sufficient to make this paper timely and enclose a credit card form for the appropriate fee. The Commissioner is authorized to charge any additional fees or credit any overpayment associated with this paper to Deposit Account No. 15-0610.

Claims 1-7 are rejected under 35 USC § 103 as unpatentable over Cheung et al. in view of Alvarez Vallina alone or with other references. The Examiner stated that the declaration previously submitted was insufficient but that it would be persuasive if all applicants signed. Applicants now enclose corresponding declarations signed by the remaining inventors. Thus, consistent with the Examiner's remarks, these rejections are believed to be overcome. Similarly, the outstanding rejection for obviousness-type double patenting is also dependent on the Alvarez-Vallina reference. Thus, this rejection is also believed to be overcome.

I hereby certify that this paper and any attachments named herein are being deposited with the US Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on April 9, 2003.

Marina T. Larson

Marina T. Larson, PTO Reg. No. 32,038

April 9, 2003
Date of Signature

Claims 1-2 were rejected under 35 USC § 102 as anticipated by Alvarez-Vallina. In view of the Examiner's comments, the submission of the enclosed declarations is believed to overcome this rejection.

Claims 1 and 2 stand rejected under 35 USC § 102(b) as anticipated by Eshhar (WO 93/19163). As previously noted, Eshar contains minimal examples, none of which relate to CD28 containing fusions. Applicants have therefore argued that Eshar is not enabling of CD28, and therefore cannot be relied upon as anticipatory of the present claims. In response, the Examiner asserts that the mere mention of CD28, combined with a disclosure of a scFV-CD16 fusion is enough to provide an enabling disclosure. No indication of similarities between CD28 and CD16 are given, nor any reasoning beyond the bare assertion are given. This is not sufficient to establish a sound basis for the stated assertion of the Examiner.

CD16 is a receptor that binds to complexed IgG to stimulate NK killer activity. In contrast, CD28 stimulates T cell activation. Eshar provides an example (Fig. 19) of a construct in which a portion of the **α-subunit** of CD16, CD16, is used with an scFv to make a fusion protein. CD28 does not have multiple heteromeric subunits so it is not apparent how this teaching would be applied in the context of CD28. Indeed, the Examiner has not offered any reasons why CD16 and CD28 would be deemed so similar by a person skilled in the art that the characteristics of a fusion incorporating CD16 would offer any expectations about likelihood of success, or a teaching of how to accomplish a functional fusion with the other.

It is also ironic that the scope of enablement which the Examiner states is provided by the reference far exceeds the scope of enablement which the Examiner originally acknowledged for this application. In the Office Action dated 1/27/00, the Examiner offered various reasons for lack of enablement of the pending claims, including that the construct needs to be in the proper orientation for signaling function of CD28, and that there are no working examples in the allegedly unpredictable art. (Page 10). Eshar's disclosure with respect to CD28 is nothing more than a listing of multiple possible receptor's and can in no way be deemed to meet the standards for enablement which the Examiner asserted were appropriate.

The Examiner has also not responded to Applicants argument that a reference, in order to function as a reference under § 102 must not only provide the equivalent of a **written description** as defined in 35 USC § 112, first paragraph, of the allegedly anticipated invention. Standards now being applied to biotechnology inventions may require actual reduction to practice to establish that an applicant was in actual **possession** of the invention. If Applicants cannot file a patent and successfully protect an invention until they known the full sequence (or close to it), it stands to reason that a reference that fails to meet this standard cannot serve as an anticipatory reference. Otherwise, one could anticipate the fields of research with nothing more than a computer generated catalog of combinations and permutations of subparts.

The Patent Office and the courts have advanced the policy that disclosure of partial nucleotide sequences and a method of how to proceed from there, even if enabling, is not sufficient to provide written description support for certain types of biotechnology inventions. The Eshar reference does not even provide this level of teaching with respect to the CD28 fusions. Instead, it says only that other fusions besides the exemplified γ and ζ-containing fusions can be made, and includes CD28 as one of a list of possible choices.

Application of this concept in this case clearly comports with fundamental fairness. The actual examples in Eshar relate to fusions containing two types of T-cell receptor (TCR) chains. These receptors are involved in generating an activation signal based on interaction with adjacent chains that physiologically associate with the TCR. In contrast, CD28 must interact with a ligand (B7) displayed on B cells and other professional antigen presenting cells or dendritic cells and macrophages, and produces a multiplicity of effects. Without actually making such fusions and performing experiments, one could not know whether or not the expressed CD28 (assuming a given fusion provided expression) would associate with supramolecular complexes as does the native protein, nor could it be known whether of not the CD28 fusion would provide all of the functionality of native CD28. For these reasons, Applicants submit that Eshar neither showed that he was in possession of the invention **(written description requirement)** as presently claimed nor placed the public in possession of the

invention as claimed (**enablement**). Thus, the anticipation rejection based on Eshar should be withdrawn

The Examiner also rejected claims 1-7 as obvious over the combination of Eshar with Fousar (claims 1-3) and additionally Sambrook (claims 1-7). In the additional comments provided in the present Office Action, the Examiner has stated that the because "monoclonal antibodies against GD2 and GD3 potentiate lymphocyte response" one would be motivated to make an anti-GD2 antibody for tumor, and "in view of Eshar who teaches fusion proteins with CD28 it would be obvious to produce the claimed polynucleotide." (Page 5) Applicants respectfully submit that this additional explanation indicates that the Examiner is merely finding parts in the art and not looking at whether the art fairly suggests combining these parts as in the claimed invention. The Examiner further argues that because Fousar teaches combination of the antibody with a cytokine "one would be motivated to combine the antibody with the cytokine of CD28 in a fusion protein." (Page 6)

In Fousar, the target cells (for example tumor cells) express GD2 on their surface. These cells are subject to cytotoxic attack in the presence of the anti-GD2 antibody. This attack can be assisted by the coadminstration of a cytokine. In contrast, the anti-GD2 antibody which can be used in the present invention is not administered as an antibody, nor does it ever form a circulating antibody. Rather, because it is part of a fusion, it becomes an artificial receptor which renders T-cells expressing the fusion subject to stimulation by GD2. In addition, it appears that the Examiner believes that CD28 is a cytokine. This is not the case. Furthermore, the cytoplasmic portions are not secreted (which is required for a cytokine) or they would loose their activating/signaling function. Thus, it appears that the reasons for combining the references are flawed.

The Sambrook reference adds no specific teachings to those of Eshar and Fouser, only general methodologies. Thus, the rejection of claims 1-7 based on these references should be withdrawn.

The Examiner rejected claims 1-2 as anticipated by Roberts (US 5,686,281). This patent discloses fusions of an extracellular binding domain, a transmembrane domain and a

signaling domain which may be derived from CD28. The patent asserts that essentially anything with binding function can serve as the extracellular binding domain, and specifically mentions scFv as a possibility. However, the patent provides no specific examples of scFv-containing fusions nor any specific teaching of how to make such fusions specifically. It also provides no evidence that such fusions function as asserted, nor any relationship besides binding function between scFv and the extracellular domains that are said to work. Thus, this patent must be scrutinized to see if it actually provides an enabling disclosure and a written description of applicants invention, or merely a generalized statement submitted to justify a generic claim, but which could never support a claim as specific as that now pending. Applicants submit that the disclosure does not survive such scrutiny, and that this rejection should therefore be withdrawn.

The Examiner also rejected claims 1-7 as obvious over the combination of Roberts with Fouser and Sambrook. This rejection suffers from the same deficiency discussed above, in that the anti-GD2 antibodies of Fouser are used for an entirely different purpose. Thus, this rejection should also be withdrawn.

Favorable reconsideration of the application in view of the remarks herein is respectfully requested.

Respectfully submitted,

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